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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,795	11/13/2003	Rosanne Crooke	ISIS.003CP1	6394

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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 04/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,795	CROOKE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *109-192* is/are pending in the application.

4a) Of the above claim(s) *146-192* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4-04-05; 6-13-05; 10-03-05; 1-05-06; 4-04-06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Inventorship

1. In view of the papers filed 3-03-06, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by adding Susan Freier as an inventor.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Information Disclosure Statement

2. The information disclosure statement filed 4-04-2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. With the exception of the US Patent documents, the remaining information referred to therein has not been considered.

3. According to Applicant's, submission on 4-04-05, the cited documents were no provided since they were previously submitted to the Patent Office in application no. 10/147,196, on which the instant application relies on for priority. However, the instant application does not rely on application 10/147,196 for priority. See 37 CFR § 1.98(d), which recites:

(d) A copy of any patent, publication, pending U.S. application or other information, as specified in paragraph (a) of this section, listed in an information disclosure statement is required to be provided, even if the patent, publication, pending U.S. application or other information was previously submitted to, or cited by, the Office in an earlier application, unless:

(1) The earlier application is properly identified in the information disclosure statement and is relied on for an earlier effective filing date under 35 U.S.C. 120; and

(2) The information disclosure statement submitted in the earlier application complies with paragraphs (a) through (c) of this section.

Election/Restrictions

4. Applicant's election of Group I, drawn to compounds and targeted to a nucleic acid encoding apolipoprotein B, in the reply filed on 2-07-06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).\

5. In a discussion with Francis Putkey on 2-14-06, she stated that elected Group I should include claims 109-145, and Group II should be drawn to claims 146-192. The response filed 2-07-06 incorrectly stated that Group I corresponds to claims 109-141, and that Group II was drawn to claims 142-192.

6. Therefore, Claims 146-192 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/07/06.

7. Claims 109-145 are presently under examination.

Specification

Sequence Information

8. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. There are sequence disclosures on page 206 of the specification as filed that have not been assigned an appropriate sequence identifier. The target sequence described in Table 33 for the Monkey and Mouse species do not appear in the Sequence Listing. The target sequence for ISIS 301012 is included in the specification as filed as SEQ ID NO: 660 (corresponds to nucleotides 3248-3267 of SEQ ID NO: 3). However this sequence appears to be in error, since SEQ ID NO: 247 is complementary to nucleotides 3249-3268 of SEQ ID NO: 3.

A complete response to this Office Action requires that Applicants comply with the sequence rules, and that pending rejections be addressed. Any response that does not address all of these issues will be held as non-responsive.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 109-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New matter rejection).

Instant claim 109, and those claims dependent therefrom recite:

109. (New) An antisense compound 12 to 30 nucleobases in length, wherein said compound specifically hybridizes with up to two mismatches to a sequence in the range of nucleotides 3230-3288 as set forth in SEQ ID NO:3.

According to Applicants, support for the instant invention can be found in the specification as filed on page 206, Table 33, and on pages 223-224, Table 44 and the following paragraph. However, the portions of the specification to which Applicants are referring are specifically drawn to antisense compounds of 20 nucleobases in length, comprising two or more mismatches, which hybridize to nucleotides 3248-3267 of SEQ NO: 3. The instant claims are drawn to antisense compounds that specifically hybridize with up to two mismatches to *a sequence* in the range of nucleotides 3230 through 3288 of SEQ ID NO: 3. The description in the specification as filed, referred to Applicants as support for the instant amendment to claim 109, does not support wherein antisense compounds are designed to specifically hybridize to *a sequence* beyond that of nucleotides 3246-3267, wherein said antisense compound comprises up to two mismatches with said sequence.

Applicant's amendment is therefore considered new matter. Applicants must cancel the new matter in response to this Office Action.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 109-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Olek et al. (WO 2001077384 A2; German language patent, 10-18-2001; citations are given from the English language equivalent US 2004/0241651 A1).

Olek et al. discloses 2 oligonucleotides of 13 nucleobases in length comprising an 11 base pair contiguous stretch of nucleotides that are 100% complementary to nucleobases 3278 through 3288. The oligonucleotides of Olek et al. that meet the above criteria are set forth in SEQ ID NO: 10587 (G-T-A-T-A-T-T-T-G-A-A-T-T), and SEQ ID NO: 166481 (T-T-T-A-T-A-T-T-T-G-A-A-T).

The invention of Olek et al. include wherein the above sequences are peptide nucleic acid (PNA) oligomers, see for example, the Detailed Description which states:

> In another variant of the method, the set of oligomer probes (oligonucleotides and/or PNA oligomers) for the detection of single nucleotide polymorphisms and/or the state of cytosine methylation in chemically pretreated genomic DNA comprises at least 100 oligonucleotides or PNA sequences selected from the sequences SEQ-ID: 1 to SEQ-ID: 382046, or, however at least 100 PNA oligomers or oligonucleotide sequences, which in turn contains the sequences listed therein, namely the sequences SEQ-ID: 1 to SEQ-ID: 382046.

13. Claims 109-115, 117-118, 120-126, 129-132, 134-135, and 137-141 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al. (US Patent No. 6172216, Published January 9, 2001).

14. Bennett et al. discloses an antisense oligonucleotide 20 nucleobases in length (SEQ ID NO: 22), wherein said antisense oligonucleotide comprises 13 identical nucleobases with SEQ ID NO: 247 of the instant application. SEQ ID NO: 22 of Bennett et al. comprises a region of 9 contiguous nucleobases that are 100% complementary to nuclebases 3258-3268 of SEQ ID NO: 3 of the instant application.

ISIS No. 16000, see col. 29, Table 3, has the sequence as set forth in the antisense oligonucleotide of SEQ ID NO: 22 (as described above), wherein said antisense oligonucleotide is a chimeric oligonucleotide, comprising wherein positions 1-5 and 16-20 comprise a 2'-MOE modification (other positions comprise 2'-deoxy modifications), all 2'-MOE cytosines are 5-methylcytosines, and all linkages are phosphorothioate linkages.

Bennett et al. also teach wherein the antisense compounds of their invention comprise sodium salts, see for example, col. 11, lines 14-23. Additionally, the invention of Bennett et al. also includes compositions comprising the disclosed antisense compounds in combination with a pharmaceutically acceptable carrier or diluent, see col. 14.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 109-126, and 129-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. as applied above, in view of Petersen et al. (May 2002).

The discussion of Bennett et al. as set forth above is incorporated here, however, Bennett et al. do not teach the incorporation of bicyclic modified sugar bases into the structure of their disclosed antisense compounds.

Petersen et al. provides a review of the benefits of designing antisense compounds to comprise sugar modifications that favor an *N*-type conformation, e.g. 2'-O-alkyl modified riboses. However, according to Petersen et al. little is known about the features underlying the increase in thermostability facilitated by these nucleotides, and at present, no structure-activity relationship exists paving the way for rational design of modified nucleic acids." (See page 5974, 2nd column) Petersen et al. teaches that LNA modifications provide a means for the rational design of modified nucleic acids. However, describes the benefits of modifying antisense compounds to comprise bicyclic sugar bases, or more specifically LNAs (bicyclic ribonucleosides monomers). According to Petersen et al. Antisense compounds comprising LNAs possess a number of prerequisites of an attractive AO, e.g. stability toward 3'-exonucleolytic degradation, and effective delivery into cells by Lipofectin mediated transfection. Fully modified LNA, and mix-mer LNA antisense oligonucleotides display unprecedented binding affinity toward complementary RNA or DNA. LNA shows no significant sequence dependence in the increased binding affinities and therefore provides an excellent tool for targeting any

RNA or DNA sequence for use both as an antisense oligonucleotide and in diagnostic applications. (See page 5975, Chart 1, and first column).

It would have been obvious to the ordinary skilled artisan at the time of the instant invention to modify the antisense compounds of Bennett et al. to comprise bicyclic nucleoside monomers (LNA). One of ordinary skill in the art at the time of the instant invention would have been motivated to make this modification since the prior art teaches that antisense compounds comprising LNA modifications produces antisense compounds with stability towards 3'exonucleolytic degradation, effective delivery into cells, and display unprecedented binding affinity to both RNA and DNA. Moreover, according to Petersen et al. their studies allow for the rational design of antisense compounds comprising LNA modifications due to their the detailed understanding of the structural features of LNA underlying its remarkable properties (see page 5975, 2nd col.).

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 109-141 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of copending Application No. 10/920,612. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and those of the copending application are drawn to antisense compounds that specifically hybridizes with nucleobases 3230-3288 as set forth in SEQ ID NO: 3. The instant claims differ from the copending claims to the extent that they are drawn to antisense compounds that are 12 to 30 nucleobases in length, and those of the copending application comprise antisense compounds that are 8 to 50 nucleobases in length. However, it is clear from the specification of the copending application that the range of 12 to 30 nucleobases is an obvious alternative embodiment of their claimed invention, see for example, page 21, 2nd paragraph.

19. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

20. Claims 142-145 are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Janet L. Epps-Ford
Primary Examiner
Art Unit 1633

JLE